Risk of Lung Cancer and Exposure to Industrial Acids, Solvents, and Metals in Leningrad Province, Russia

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Objective: *We sought to investigate the association of occupational exposure to industrial acids, solvents, and metals with lung cancer in Leningrad Province, Russia, where an excess of occupationally related lung cancer was reported recently.* ***Methods:*** *We identified 540 pathologically diagnosed lung cancer cases and 582 controls from the 1993–1998 autopsy records of the 88 Leningrad Province hospitals. Lifetime job-specific exposure measurements were available for 12 industrial acids, 15 solvents, and 17 metals.* ***Results:*** *Exposures were frequent in the study group and mostly occurred after World War II. However, lung cancer risks for industrial acids (odds ratio [OR] = 1.2; 95% confidence interval [CI] = 0.8–1.7), solvents (OR = 0.8; 95% CI = 0.6–1.2), and metals (OR = 0.8; 95% CI = 0.5–1.0) were not increased. Also, no significant excess risk was found for any of the specific agents investigated.* ***Conclusions:*** *The excess of occupationally related lung cancer in the Province is not explained by exposure to the agents investigated.* (J Occup Environ Med. *2006;48:48–55*)

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Lung cancer is the most frequent malignant neoplasm in industrialized countries.[1] According to the World Health Organization, occupational exposures may account for approximately 10.3% of lung cancer cases worldwide.[2] We recently conducted a case–control study on lung cancer risk in Leningrad Province, Russia, an area with a population of 1.5 million subjects, that showed an excess risk of lung cancer for workers in the manufacturing industry relative to subjects in other employment sectors.[3] To identify carcinogenic exposures determining such lung cancer excess, we furthered our investigations in the same study group by examining exposure in work facilities of the study area to industrial acids, solvents, and metals in relation to lung cancer risk. To this end, we took advantage of a centralized monitoring and reporting system for occupational exposures that has been operating in the Province.

Exposure to several industrial acids, solvents, and metals has been established or suggested as etiologic factor for lung cancer,[4–7] as well as for other neoplastic and non-neoplastic diseases.[8–10] The International Agency for Research on Cancer (IARC) has classified as carcinogenic to humans, with specific reference to lung cancer, a number of agents, including sulfuric acid mists,[11] chloromethyl ethers,[12] arsenic and arsenic compounds,[12] beryllium and beryllium compounds,[13] chromium [VI],[14] nickel compounds,[14] and cadmium and cadmium compounds.[13] Less-consistent data exist

for other agents, such as toluene,[6,15] trichloroethylene,[16] tetrachloroethylene,[17] benzene,[6] lead,[18] cobalt,[19] iron,[9] and molybdenum.[9] After the 1992 IARC evaluation of acid mists carcinogenicity,[11] increased lung cancer risk also was observed in female subjects who reported occupational exposure to sulfuric and/or hydrochloric acid in a case–control study conducted in Poland.[20]

Solvents as single agents have been extensively studied for induction of cancer in experimental animals, but none of the agents is considered overtly genotoxic.[6]After positive bioassays reports for bis (chloromethyl) ether, high risk of lung cancer was reported among chemical workers exposed bis (chloromethyl) ether and chloromethyl methyl ether during the manufacture of ion exchange resins.[21] Moderate excess risk of lung cancer was described in subjects exposed to toluene in rotogravure printing[15,22] and shoe manufacturing.[23] However, toluene has been found to be nonmutagenic and nongenotoxic in experimental studies.[8] For other organic solvents, evidence for lung carcinogenicity in humans is more subtle.[6]

Studies on highly exposed occupational groups, together with some investigations of populations with unusual exposure, have indicated carcinogenic properties for several metals.[9] Increased risks for lung cancer have been linked to arsenic exposure in cohort studies on smelter workers[24] and arsenical pesticide manufacturers.[25]

Although beryllium exposure was associated with lung cancer in several investigations,[13] a later reanalysis of one of these studies indicated lower and generally not statistically significant mortality ratios than originally reported.[26] Similarly, at variance with previous epidemiological evidence that demonstrated an association between occupational exposure to cadmium and lung cancer,[13] a recent study in UK nickel–cadmium battery workers did not find a significant association between exposure to cadmium compounds and lung cancer mortality.[27] Recent investigations confirmed that lung cancer risk is increased among chromate production workers[28–30] and chromium platers.[31,32] Although nickel exposure has been associated with lung cancer in several epidemiology studies of nickel miners, smelters, electrolysis workers, and high-nickel alloy manufacturers,[14] debate still exists on whether all nickel compounds are carcinogenic for humans. We report here results on the association of lung-cancer risk with occupational exposure to industrial acids, metals, and solvents in the case-control study we conducted in Leningrad Province.

Materials and Methods

Study Subjects

From the 1993–1999 autopsy records of the St. Petersburg Central Pathology Laboratory, which collects reports on all autopsies performed in the Province, we identified 540 pathologically diagnosed lung cancer cases (474 men and 66 women), and 582 controls (453 men and 129 women) selected among deceased subjects with autopsy-based diagnosis of noncancer diseases, as previously described.[3] In Leningrad Province, postmortem examinations are performed on approximately 95% of the subjects who die in the 88 local state hospitals. Control subjects were frequency-matched to the cases by age (in 5-year groups), gender, and geographical area (17 regions). Procedures for frequency-matching by gender required the selection of a number of female controls double than that of female cases. The causes of death of the control subjects were infectious diseases (ICD-9 009, 011, 038; 1.4%); diabetes and other pancreatic disorders (ICD-9 250, 251; 0.9%); anemia and other blood diseases (ICD-9 280, 285, 289; 1.0%); diseases of the nervous system (ICD-9 320, 348.5, 348.9; 15.3%); ischemic heart disease (ICD-9 410, 411; 7.9%); diseases of pulmonary circulation (ICD-9 415, 416; 4.8%); diseases of pericardium (ICD-9 423; 2.2%); heart failure (ICD-9 428; 33.0%); cerebrovascular disease (ICD-9 430, 431, 434; 7.2%); other disorders of the circulatory system (ICD-9 452, 456, 394.1; 0.5%); pneumonia and influenza (ICD-9 482, 485, 486; 6.4%); other diseases of lung and respiratory system (ICD-9 518, 519.2; 0.7%); diseases of the digestive system (ICD-9 520–579, 9.6%); diseases of the genitourinary system (ICD-9 580–599, 3.4%); symptoms involving cardiovascular system (ICD-9 785, 2.9%); injuries (ICD-9 994–996, 0.3%); and other disorders and symptoms (ICD-9 682.2, 780, 799.1, 799.4, 799.8; 2.4%).

In control subjects, we evaluated several variables that may have influenced inclusion into the study. High proportions of controls had held jobs in productive sectors (Table 1), such as manufacturing, construction, and agriculture industries, as it was expected on the basis of the economic characteristics of Leningrad Province. As we previously reported,[3] smoking proportions among controls in our study were similar to those recorded in Russia,[33] suggesting that smokers were not more likely to be part of our control group than non-smokers. Also, marital status and education level distribution did not provide evidence that major selection mechanisms may have operated. The date of birth of the study subjects varied between 1902 and 1977 (median year of birth = 1932). The year of first employment was between 1922 and 1991 (median = 1951), and the year of the end of work activity between 1946 and 1999 (median = 1993). Median age at first employment was 18.0 years (inter-quartile range: 17.0–19.6). Median age at the end of work activity was 59.4 years (interquartile range, 54.7–62.7).

We obtained health-related data, including information on smoking, from local health services and hygiene centers that routinely use standardized protocols to record them.

TABLE 1
Characteristics of the Study Subjects

	All Subjects		Men		Women	
	Cases (n = 540)	Controls (n = 582)*	Cases (n = 474)	Controls (n = 453)*	Cases (n = 66)	Controls (n = 129)*
Age						
21–45 yr	39 (7.2%)	34 (5.8%)	35 (7.4%)	29 (6.4%)	4 (6.1%)	5 (3.9%)
46–55 yr	68 (12.6%)	70 (12.0%)	60 (12.7%)	59 (13.0%)	8 (12.1%)	11 (8.5%)
56–65 yr	218 (40.4%)	225 (38.7%)	203 (42.8%)	189 (41.7%)	15 (22.7%)	36 (27.9%)
66–86 yr	215 (39.8%)	253 (43.5%)	176 (37.1%)	176 (38.9%)	39 (59.1%)	77 (59.7%)
Smoking						
Never	61 (11.4%)	190 (32.9%)	13 (2.8%)	90 (20.0%)	48 (72.7%)	100 (78.1%)
<1 pack/d	208 (38.7%)	217 (37.5%)	197 (41.8%)	194 (43.1%)	11 (16.7%)	23 (18.0%)
≥1 pack/d	268 (49.9%)	171 (29.6%)	261 (55.4%)	166 (36.9%)	7 (10.6%)	5 (3.9%)
Industry†						
Agriculture and fishing	181 (12.9%)	184 (13.0%)	169 (13.1%)	146 (12.4%)	12 (10.5%)	38 (15.9%)
Construction	151 (10.7%)	145 (10.2%)	143 (11.1%)	126 (10.7%)	8 (7.0%)	19 (7.9%)
Transportation	122 (8.7%)	114 (8.0%)	116 (9.0%)	94 (8.0%)	6 (5.3%)	20 (8.4%)
Manufacturing	349 (24.8%)	331 (23.4%)	307 (23.8%)	260 (22.1%)	42 (36.8%)	71 (29.7%)
Services	234 (16.6%)	288 (20.3%)	199 (15.4%)	210 (17.8%)	35 (30.7%)	78 (32.6%)
Ministry of Defense	369 (26.2%)	355 (25.1%)	358 (27.7%)	342 (29.0%)	11 (9.6%)	13 (5.4%)

*Control subjects were frequency matched to the cases by age, gender, and residence. Procedures for frequency-matching by gender required the selection of a number of female controls approximately double than that of female cases.

†Subjects may have worked in one or more industry categories during their lifetime. Therefore, the total number of subjects is lower than the sum of the subjects in the individual categories.

The study protocol was reviewed and approved by the Institutional Review Board of the participating Institutions.

Exposure Assessment

Local hygiene centers have periodically and routinely obtained monitoring data from all the work facilities in Leningrad Province on nearly 280 exposures, including industrial acids, solvents, metals, dusts, fibers, gaseous agents, aromatic hydrocarbons, complex mixtures, other industrial chemicals, agricultural chemicals, physical agents, psychological agents, ergonomic factors, and biological agents. For the present study, we reviewed the hygiene-center records to obtain specific exposure data on 12 industrial acids, 15 solvents, and 17 metals for all the jobs held by the subjects in our study. For each subject, individual information on job title, work location, work area, and start and end dates obtained from lifetime work history records[3] were used to identify relevant exposure measurement data collected in the archives of the hygiene centers. Relevant exposure data were those performed in a work-area during the period a study subject had been working in it.

The exposure measurements were evaluated by 17 occupational physicians (ie, one from each of the regions in the province) with specific expertise in the assessment of historical workplace exposures. The physicians received specific training for the study by an investigator (M.D.) from the U.S. National Cancer Institute to ensure accurate and standardized exposure assessment procedures. If exposure measurements for a study subject's job were unavailable or not sufficiently detailed at the hygiene centers, the physicians visited the employment site to obtain additional exposure information from the factory archives. Measurements usually were based on full-shift stationary measurements routinely performed to comply with hygiene regulations. Less frequently, personal measurements were available. Stationary and personal measurements were consistent as to whether subjects were exposed, with usually moderate intensity differences. Each exposure was classified with respect to its presence, intensity, frequency, and duration. For each exposure, a confidence score reflecting the degree of certainty in the information retrieved (from 1 = low to 4 = very high) was assigned. When exposure data with low confidence scores were excluded, results were similar to those obtained from the analysis on the entire exposure data set. The exposure intensity for a 40-hour workweek was estimated on the basis of work-area measurements and categorized using the following score system: nonexposure, score = 0; <50% of the Russian Maximum Allowable Concentration (MAC),[34] score = 0.25; ≥50% but <100% MAC, score = 0.75; and ≥100% MAC, score = 2.25.

The occupational physicians were asked to estimate the usual exposure intensity present in the work area and discarded any exposure measurement that was likely to have been performed in a worst-case scenario. MAC values were used as the reference to standardize across all potential exposures. The score of 2.25 for concentrations ≥100% MAC was assumed to better reflect the likely log-normal or positively skewed dis-

tribution of the agent concentrations. The average intensity score of a specific exposure was calculated as the time-weighted mean of intensity scores across all jobs in which the exposure had occurred. The cumulative exposure score was calculated as the product of average intensity score times total duration of exposure. For the analysis, we categorized average intensity scores into two groups: 1) <0.75 (ie, <75% MAC) and 2) >0.75 (ie, ≥75% MAC). Similarly, we categorized the exposed subjects in two groups of duration (<10 years and ≥10 years), and cumulative exposure (score <5 and score ≥5). MAC air values and average intensities for exposed cases and controls, estimated from average intensity scores, are reported in the Appendix. For aggregated exposure groups including more than one single agent, such as the industrial acids, organic acids, inorganic acids, acids (origin unknown), solvents, aromatic solvents, other solvents, Metals, or not-elsewhere-classified (n.e.c.) categories, we calculated mean durations, mean duration-weighted intensity scores, and mean cumulative exposure scores.

Statistical Analysis

We used unconditional multiple logistic regression analysis to compute odds ratios (ORs) and 95% confidence intervals (CIs) adjusted for age, gender, and smoking (never, not every day, <20 cigarettes/day, ≥20 cigarettes/day). Models including region of residence produced results similar to those from models adjusted only by age, smoking, and gender. ORs for lung cancer were calculated for exposures with five or more lung cancer cases. All the analyses were performed using Stata 8.0 (Stata Corp., College Station, TX).

Results

Characteristics of the Study Subjects

Median age was 63 years (range: 33–86 years) for male and 68 years (range: 22–84 years) for female lung cancer cases; 37.1% of the male cases and 59.1% of the female cases were older than 65 years of age (Table 1). Male subjects exhibited a high prevalence of smoking; 36.9% of the controls were heavy smokers (one pack of cigarettes a day or more) and 43.1% were light smokers (<one pack/day; Table 1). Among the male cases, we found 55.4% and 41.8% of heavy and light smokers, respectively. The age-adjusted OR for lung cancer was 11.3 (95% CI = 6.1–21.0) for heavy and 7.3 (95% CI = 3.9–13.5) for light male smokers. The proportion of smokers was lower in the female population (3.9% heavy and 18.0% light smokers in controls; 10.6% heavy and 16.7% light smokers in cases). In females, the age-adjusted OR for lung cancer was 3.0 (95% CI = 0.9–10.3) for heavy and 0.9 (95% CI = 0.4–2.1) for light smokers. The average lifetime number of jobs was 4.3 in lung cancer cases and 4.1 in controls. The most frequent sectors of employment in this study group were the manufacturing industry, services, and Ministry of Defense (Table 1). The number of subjects exposed varied by calendar time, with most of the occupational exposures relevant for the present study taking place after World War II (Fig. 1).

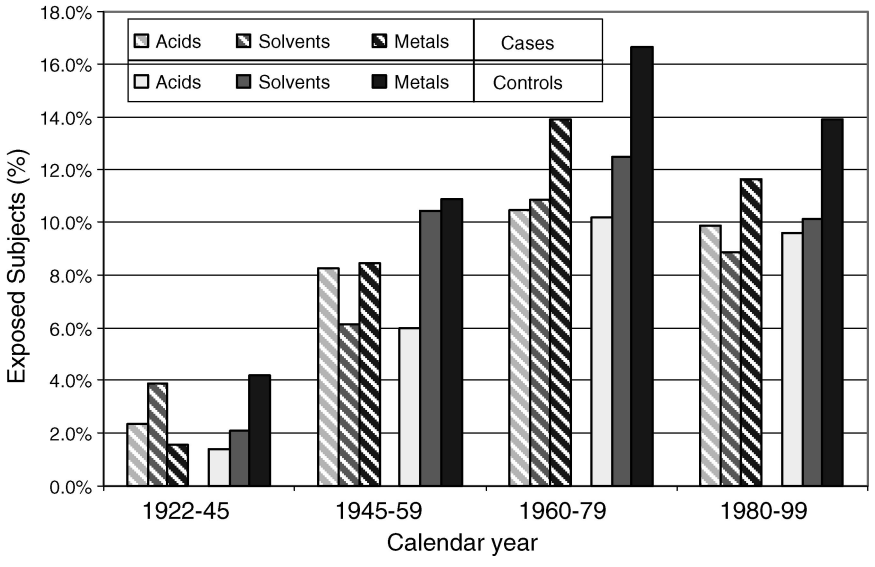

Fig. 1. Proportions by calendar period of active male and female workers (cases and controls) exposed to industrial acids, solvents, and metal.

Risk of Lung Cancer Among Subjects Exposed to Industrial Acids, Solvents, and Metals

Seventy-nine lung cancer cases and 75 controls were ever exposed to industrial acids. The OR for lung cancer associated with exposure to industrial acids was 1.2 (95% CI = 0.8–1.7; Table 2). Within subjects ever exposed to industrial acids, no major differences in lung cancer risk were observed between exposure to organic (OR = 1.5, 95% CI = 0.6–3.5) and inorganic acids (OR = 1.2, 95% CI = 0.8–1.8). A moderate, not significant increase in lung cancer risk was observed in subjects ever exposed to sulfuric acid (OR = 1.4, 95% CI = 0.9–2.2), but no consistent trends were found in the analysis by duration, average intensity and cumulative exposure (Table 3). Workers exposed to nitric acid exhibited a not significant excess risk (OR = 8.1, 95% CI = 0.9–76.7), based on five cases and one control, only.

TABLE 2
Occupational Exposure to Industrial Acids, Solvents, or Metals and Risk of Lung Cancer in Leningrad Province, Russia

Exposure	Case (n = 540)	Control (n = 582)	OR*	(95% CI)*
Industrial acids	79	75	1.2	(0.8–1.7)
Organic acids	14	11	1.5	(0.6–3.5)
Acetic acid	8	10	0.9	(0.4–2.6)
Carbonic acid	5	1	4.8	(0.5–43.6)
Organic acids, n.e.c.†	3	1	—‡	—‡
Inorganic acids	69	64	1.2	(0.8–1.8)
Sulfuric acid	46	37	1.4	(0.9–2.2)
Hydrogen fluoride	21	25	0.9	(0.5–1.8)
Hydrogen chloride	12	12	1.4	(0.6–3.2)
Nitric acid	5	1	8.1	(0.9–76.7)
Inorganic acids, n.e.c.†	0	2	—‡	—‡
Acids, origin is unknown	2	5	—‡	—‡
Solvents	70	88	0.8	(0.6–1.2)
Aromatic	42	51	0.9	(0.6–1.4)
Toluene	32	39	0.9	(0.5–1.4)
Xylene	21	30	0.7	(0.4–1.4)
Benzene	14	16	1.1	(0.5–2.3)
Styrene	9	24	0.4	(0.2–0.8)
Aliphatic	5	4	1.5	(0.4–6.1)
Others	38	57	0.7	(0.4–1.1)
Acetone	23	36	0.7	(0.4–1.2)
White spirit	23	28	0.9	(0.5–1.6)
Butyl acetate	11	7	1.5	(0.6–4.2)
Methanol	7	7	1.0	(0.3–2.9)
Nonaromatic/nonaliphatic, n.e.c.†	7	9	1.0	(0.4–3.0)
Solvents, origin is unknown	28	31	0.8	(0.5–1.4)
Metals	92	115	0.8	(0.5–1.0)
Lead	34	60	0.5	(0.3–0.9)
Manganese	29	25	1.2	(0.7–2.1)
Copper	15	13	1.1	(0.5–2.4)
Aluminum	13	9	1.5	(0.6–3.7)
Chromium	12	13	1.2	(0.5–2.8)
Zinc	9	11	0.8	(0.3–2.1)
Nickel	7	7	1.2	(0.4–3.7)
Tin	6	11	0.7	(0.2–1.9)
Metals, n.e.c.†	8	13	0.5	(0.2–1.3)
Metals, origin is unknown	18	21	0.7	(0.4–1.4)

*ORs and 95% CIs adjusted for age, gender, and smoking using logistic regression analysis.

†Not elsewhere classified. The category includes exposures with fewer than five lung cancer cases.

‡ORs and 95% CIs were not calculated for exposure categories with fewer than five lung cancer cases.

Seventy lung cancer cases and 88 controls were ever exposed to solvents, with no increased risk for lung cancer (OR = 0.8, 95% CI = 0.6–1.2). No association with lung cancer was observed for aromatic (OR = 0.9, 95% CI = 0.6–1.4), aliphatic (OR = 1.5, 95% CI = 0.4–6.1), or other solvents (OR = 0.7, 95% CI = 0.4–1.1), as well as for any of the individual agents.

Exposure to metals (92 ever-exposed lung cancer cases; 115 ever-exposed controls) was associated with an OR of 0.8 (95% CI = 0.5–1.0). No significant excess risks were observed for exposures to any of the single metals evaluated (Table 2).

We evaluated lung cancer risk by duration, average intensity, and cumulative exposure score for the exposure categories that included ten or more lung cancer cases. In this analysis, we did not observe any significant association between the chemicals evaluated and lung cancer risk (Table 3).

We repeated all the analyses by stratifying the study subjects according to their smoking history and no major differences in risk estimates for smokers and non-smokers were found. Also, no differences were observed when data were stratified by gender or time since first exposure, or when all exposures occurred within 10 years from the subjects' death were excluded. No major differences in risk estimates for industrial acids, solvents and metals were observed when analyses were stratified according to whether exposure had occurred within the manufacturing industry, which was associated with increased lung cancer risk in previous analyses based on job-title.[3]

Discussion

The present study was based on extensive exposure information derived from concentration measurements of a large number of industrial acids, solvents, and metals, including several established or potential lung carcinogens. The availability of exposure measurements over a wide time span allowed us to reconstruct lifetime exposure profiles for each of the study subjects.

Risk of lung cancer was not significantly associated with exposure to industrial acids, solvents and metals in our study. Some of our exposure categories, such as chromium and nickel (Table 2), included a combination of agents with established lung carcinogenic properties such as chromium [VI] or nickel compounds together with other agents with uncertain or no carcinogenicity (eg, metallic chromium and chromium[III] compounds; metallic nickel).[9,14] This, together with the small number of observations for some of the agents evaluated, may have contributed to the lack of association with lung cancer risk in our results. Also, sulfuric acid was not significantly asso-

TABLE 3
Risk of Lung Cancer by Duration, Average Intensity, and Cumulative Exposure to Acids, Solvents, and Metals in Leningrad Province, Russia

Exposure	Duration				Average Intensity				Cumulative Exposure Score			
	<10 yr		≥10 yr		<75% MAC		≥75% MAC		<5*		≥5*	
	OR†	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Industrial acids	1.5	(0.8–2.6)	1.1	(0.7–1.7)	1.2	(0.8–1.9)	1.2	(0.7–2.1)	1.6	(1.0–2.7)	0.9	(0.5–1.4)
Organic acids	1.1	(0.3–3.9)	1.9	(0.6–6.0)	1.3	(0.4–3.8)	1.9	(0.5–7.1)	1.7	(0.5–5.9)	1.3	(0.4–4.1)
Acetic acid	0.7	(0.2–2.9)	1.3	(0.3–5.4)	1.1	(0.3–3.8)	0.7	(0.1–3.9)	1.3	(0.4–4.4)	0.5	(0.1–3.1)
Inorganic acids	1.6	(0.8–3.0)	1.1	(0.7–1.7)	1.2	(0.8–2.0)	1.2	(0.7–2.1)	1.7	(1.0–2.9)	0.9	(0.5–1.5)
Sulfuric acid	2.0	(0.9–4.4)	1.1	(0.6–2.0)	1.3	(0.8–2.3)	1.4	(0.6–3.3)	1.6	(0.9–3.0)	1.1	(0.5–2.2)
Hydrogen fluoride	1.6	(0.5–5.4)	0.8	(0.4–1.6)	1.5	(0.5–4.8)	0.8	(0.4–1.6)	1.7	(0.6–5.2)	0.7	(0.3–1.5)
Hydrogen chloride	1.6	(0.5–5.1)	1.1	(0.3–4.0)	1.1	(0.3–3.7)	1.7	(0.5–5.7)	2.1	(0.6–6.7)	0.8	(0.2–3.0)
Solvents	0.7	(0.4–1.1)	0.9	(0.6–1.5)	0.7	(0.5–1.2)	0.9	(0.6–1.6)	0.7	(0.4–1.1)	0.9	(0.6–1.5)
Aromatic	0.8	(0.4–1.6)	1.0	(0.6–1.7)	0.6	(0.3–1.2)	1.2	(0.6–2.1)	0.8	(0.4–1.7)	0.9	(0.5–1.6)
Toluene	0.9	(0.4–1.9)	0.9	(0.4–1.7)	0.5	(0.2–1.3)	1.1	(0.6–2.1)	1.1	(0.5–2.6)	0.8	(0.4–1.4)
Xylene	0.4	(0.2–1.1)	1.1	(0.5–2.4)	0.6	(0.2–1.5)	0.9	(0.4–1.9)	0.6	(0.2–1.5)	0.9	(0.4–1.9)
Benzene	2.3	(0.4–14.5)	0.9	(0.4–2.1)	0.8	(0.2–2.8)	1.3	(0.5–3.4)	2.7	(0.6–11.8)	0.7	(0.3–1.9)
Styrene	0.2	(0.1–0.8)	0.5	(0.2–1.3)	0.2	(0.0–0.9)	0.5	(0.2–1.2)	0.4	(0.1–1.7)	0.3	(0.1–0.9)
Others	0.5	(0.3–1.0)	0.9	(0.5–1.6)	0.8	(0.4–1.5)	0.6	(0.3–1.2)	0.5	(0.2–1.0)	0.9	(0.5–1.6)
Acetone	0.5	(0.2–1.2)	0.8	(0.4–1.7)	0.9	(0.4–2.2)	0.6	(0.3–1.1)	0.3	(0.1–1.0)	0.9	(0.4–1.7)
White spirit	1.1	(0.4–3.1)	0.8	(0.4–1.6)	1.5	(0.6–3.9)	0.6	(0.3–1.3)	0.8	(0.3–2.5)	0.9	(0.5–1.9)
Butyl acetate	1.1	(0.3–3.8)	2.8	(0.5–15.4)	1.9	(0.5–8.1)	1.3	(0.3–5.0)	2.3	(0.5–10.0)	1.1	(0.3–4.2)
nts, origin is unknown	0.6	(0.3–1.3)	1.1	(0.5–2.4)	0.5	(0.2–1.1)	1.2	(0.6–2.5)	0.7	(0.3–1.4)	1.0	(0.4–2.2)
Metals	1.1	(0.7–1.9)	0.6	(0.4–0.9)	0.9	(0.5–1.3)	0.7	(0.4–1.0)	1.2	(0.7–1.9)	0.6	(0.4–0.9)
Lead	1.0	(0.5–2.2)	0.4	(0.2–0.7)	0.6	(0.3–1.1)	0.5	(0.3–1.0)	1.0	(0.5–2.2)	0.4	(0.2–0.7)
Manganese	2.3	(0.8–6.8)	0.9	(0.5–1.8)	1.2	(0.4–3.8)	1.2	(0.6–2.3)	1.7	(0.5–5.4)	1.1	(0.5–2.1)
Copper	0.9	(0.3–3.3)	1.2	(0.5–3.2)	1.0	(0.4–2.9)	1.2	(0.4–3.8)	0.7	(0.2–2.3)	1.5	(0.5–4.3)
Aluminum	3.0	(0.7–12.5)	0.8	(0.2–2.7)	1.3	(0.3–5.4)	1.6	(0.5–5.2)	1.5	(0.4–5.3)	1.5	(0.4–5.3)
Chromium	1.6	(0.4–6.6)	1.0	(0.3–2.9)	1.0	(0.3–4.0)	1.3	(0.4–4.0)	2.1	(0.5–8.0)	0.8	(0.3–2.5)
Metal, origin is unknown	1.4	(0.5–3.9)	0.5	(0.2–1.1)	1.1	(0.4–3.3)	0.6	(0.3–1.3)	1.9	(0.6–6.0)	0.5	(0.2–1.0)

*Cumulative exposure score was calculated as the product of average intensity score (ranging from 0.25 to 2.25) per total duration.
†ORs and CIs adjusted for age, gender, and smoking in multiple logistic regression analysis.

ciated with lung cancer risk in our study. However, point estimates for relative odds of lung cancer in exposed subjects were increased of approximately 40%, which is close to the excess risk found in previous cohort studies.[5,11,35,36] Estimated average exposure intensity for sulfuric acid in our study (approximately equal to 2.4 mg/m^3) was in the upper range of the average intensities measured in previous studies.[11] For instance, in the study by Beaumont et al.,[35] in which lung cancer risk was significantly increased, the average concentration from area measurements was 0.29 mg/m^3. Higher average exposure levels (9.1 mg/m^3) were reported by Englander et al.[37] between the years 1969–1984 in a group of exposed subjects that showed a 2-fold, non-statistically significant, increase in lung cancer risk. In our study, the relatively small number of subjects exposed to sulfuric acid limited the statistical power to detect the effects of sulfuric acid exposure.

One of the recurrent weaknesses of case–control studies stems from the difficulty of retrospectively assessing past occupational exposures, which often are quantified from interview information or through job-exposure matrices based on job titles. Our study was based on work-area measurements, which were retrieved and examined by highly qualified industrial hygiene specialists who were familiar with local workplaces and received specific training to guarantee standardized procedures for exposure-data retrieval and classification. Exposure status inferred from the measurements available was confirmed in several site visits conducted in different work facilities to verify actual exposure conditions. Because the exposure measurements covered a long time period, it was not possible to have direct information on measurement validity for past exposures. The measurements usually were based on stationary measurements. Less frequently personal measurements, which represent more accurately individual exposure, were available. Therefore, we cannot exclude that misclassification in individual exposure status, and intensity

APPENDIX

Maximum Allowable Concentrations (MAC) for the Single Agents Evaluated and Estimated Exposure Intensity in Lung Cancer Cases and Controls

Exposure	MAC Value (mg/m^3)	Average Exposure Intensity (mg/m^3)	
		Cases	Controls
Industrial acids			
Acetic acid	25	14.1	15.0
Carbonic acid	1	0.85	0.25
Sulfuric acid	5	2.35	2.40
Hydrogen fluoride	5	4.43	4.68
Hydrogen chloride	7	4.52	4.08
Nitric acid	5	4.75	1.25
Solvents			
Toluene	20	15.9	17.2
Xylene	8	6.35	7.19
Benzene	10	8.93	8.85
Styrene	10	6.39	8.60
Acetone	200	115.9	153.5
White spirit	0.1	0.08	0.08
Butyl acetate	300	225.0	289.3
Methanol	5	2.79	2.11
Metals			
Lead	0.01	0.01	0.01
Manganese	0.3	0.36	0.35
Copper	1	0.81	0.70
Aluminum	2	2.27	1.39
Chromium	1	1.08	1.17
Zinc	0.5	0.65	0.33
Nickel	0.05	0.02	0.05
Tin	0.1	0.07	0.06

may have occurred and contributed to the lack of significant findings. However, when both stationary and personal measurements were available, they were consistent as to whether subjects were exposed and showed moderate intensity differences. For intensity-based analyses, measurements were standardized to a semiquantitative scale to guarantee comparability between measurements taken at different time, by different operators, and in different work-facilities, and thus reduce misclassification. Exposure measurements were not available or not consistently assessed over time in the work facilities of the study area for some exposure of potential interest. For instance, information concerning arsenic exposure presented gaps in specific time periods. Therefore, we elected not to consider arsenic exposure in our analyses.

For the present study, lung cancer cases and nonlung cancer controls were selected among subjects who died in one of the 88 hospitals of Leningrad Province. The study subjects were identified from the autopsy records of the St. Petersburg Central Pathology Laboratory, which collects reports on all autopsies performed in the Province. In Leningrad Province postmortem examinations are performed on approximately 95% of the subjects who die in a hospital. However, because not all deaths from lung cancer occur in hospitals, selection mechanisms may have influenced the inclusion of lung cancer cases into the study. We also identified non-lung cancer subjects from the autopsy records of the Central Pathology Laboratory. Subjects admitted at the same hospitals as the cases are likely to be members of the same study base[38] and to share with the cases comparable information quality and health care seeking behavior.[39] The evaluation among controls of the distribution by education level, marital status, and industry of employment did not provide evidence that major selection mechanisms may have operated. In addition, gender-specific proportions of smokers among control subjects were comparable to the reported prevalence of tobacco use in the Russian Federation.[33] Among lung cancer cases, smoking prevalence was very high in men and lower in women, possibly reflecting lower smoking rates among women in this population, as well as underreporting by female subjects, given that, until recent years, smoking was not considered proper for women in Russia.

Conclusions

The frequency of exposure to industrial acids, solvents and metals was common in this study group. Nonetheless, no significant association with lung cancer risk was found, suggesting that the excess of occupationally-related lung cancer in the study area is not substantially explained by occupational exposure to industrial acids, solvents and metals.

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